BASELINE CD4 CELL COUNTS AND OUTCOMES AMONG ADULT TREATMENT NAÏVE HIV PATIENTS AFTER TAKING FIXED DOSE COMBINATION GPO-VIR-S AND GPO-VIR-Z IN THAILAND

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Abstract. A retrospective study was conducted by reviewing 459 medical records of adult treatment naïve HIV patients who received a fixed dose combination of GPO-VIR-S (stavudine, lamivudine and nevirapine) or GPO-VIR-Z (zidovudine, lamivudine and nevirapine) at Ramathibodi Hospital in Bangkok, Thailand during 2002-2009 following Thai National Treatment Guideline for adults with HIV. The aim of this study was to assess the association between the baseline CD4 cell count and outcome. The median CD4 cell count at baseline, 6, 12 and 102 months were 102 cells/ l, 213 cells/ l, 274 cells/ l and 423 cells/ l. The virologic response (p=0.327), virologic rebound (p=0.626), adverse effects of anti-retroviral therapy (ART) (p=0.976), switching to other ART (p=0.245), occurrence of immune reconstitution inflammatory syndrome (IRIS) (p>0.05) and occurrence of drug resistance (p=0.952) were not significantly associated with baseline CD4 count. The Kaplan-Meier estimate showed the median time (95% CI) to achieve virologic response was 10.4 (9.8-11.0) months and the median time to achieve virologic rebound was 30.0 (21.6-38.4) months after initiation of ART. Analysis showed the median time to achieved virologic response (p=0.401) and virologic rebound (p=0.562) were not significantly associated with the baseline CD4 count. This study shows the outcome after onset of ART did not vary by baseline CD4 cell count.

Keywords: HIV infection, baseline CD4 counts, antiretroviral therapy, Thailand

INTRODUCTION

The baseline CD4 cell count at initia-

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tion of antiretroviral therapy (ART) had been suggested as an important factor to achieve a better outcome among HIV patients (Egger *et al*, 2002). In the past ART was initiated in all patients with a baseline CD4 cell count <200 cells/ l (WHO, 2006). But initiation of ART at a baseline CD4 cell count <200 cells/ l may lead to a high proportion of patients with acquired immunodeficiency syndrome (AIDS) and

a high case fatality rate (Baker *et al*, 2008; Rajasekaran *et al*, 2009). Other studies have shown initiation of ART among HIV patients with a CD4 cell count >200 cells/ l results in improved survival (SMART Study Group *et al*, 2008; When To Start Consortium *et al*, 2009; Kitahata *et al*, 2009; Severe *et al*, 2010). The world Health Organization (WHO) and the Department of Health and Human Services (DHHS) in United States recommended ART should be initiated in HIV patients with a baseline CD4 cell count <350 cells/ l (DHHS, 2009; WHO, 2010). It was found patients with a baseline CD4 cell count >350 cells/ l returned to a normal CD4 cell count after initiation of ART and stayed there for up to 6 years (Moore and Keruly, 2007). Other studies have also found better virologic and immunologic outcomes when ART is initiated in patients with a baseline CD4 cell count >500 cell/ l (Garcia *et al*, 1999; Palella *et al*, 2003) and the mortality rate is similar to the general population (Lewden *et al*, 2007). In contrast, a study from India showed a high proportion of HIV patients with virologic and immunologic response after initiation of ART irrespective of the baseline CD4 cell count or viral load (Kilaru *et al*, 2006). That finding was similar to other reports that showed no difference in virologic response after initiation of ART between a baseline CD4 cell count >350 cell/ l and baseline CD4 cell count <200 cell/ l (Erhabor *et al*, 2006).

In Thailand, a low price fixed-dose combination of stavudine, lamivudine and nevirapine, called GPO-VIR-S, was produced since the 2002. GPO-VIR-Z which substitutes zidovudine for stavudine in the combination GPO-VIR-S was introduced in the year 2008 in order to reduce the side effects of stavudine including lipoatrophy and neuropathy. The Thai National Guidelines for 2010 recommend initiating ART in patients with an AIDS defining illness or in asymptomatic HIV patients with a CD4 cell count <350 cells/ l in order to reduce AIDS as well as non-AIDS related morbidity and mortality (Sungkanuparph *et al*, 2010). At present, the appropriate time for initiating ART is controversial and there is no data to support the association between the baseline CD4 cell count and outcome of an HIV patient after initiation of ART in Thailand. Therefore, we conducted a retrospective study in order to assess the association between baseline CD4 cell count and outcomes among HIV patients.

MATERIALS AND METHODS

Study patients

This retrospective study was conducted by reviewing medical records of adult treatment naïve HIV patients aged 18 years or greater who attended the outpatient clinic at Ramathibodi Hospital, Bangkok, Thailand during 2002-2009 and received a fixed dose combination of ART, namely GPO-VIR-S or GPO-VIR-Z, according to the Thai National Treatment Guidelines (Sungkanuparph *et al*, 2010), for at least 6 months. Patients who received immunosuppressive drugs or pregnancy were excluded.

Operational definitions

The baseline CD4 cell count was defined as the CD4 cell count prior to initiation of ART. Virologic response was defined as the maximal inhibition of viral replication *in vivo*, as evidenced by a sustained suppresion of plasma HIV RNA below the assay limit of detection (VL<UDL) (DHHS, 2009). After virologic suppression, repeated detection of HIV RNA above the assay limit of detection was defined as virologic rebound (DHHS, 2009). Immune reconstitution inflamma-

tory syndrome (IRIS) can occur in patients after initiation of ART and includes paradoxical IRIS and unmasking IRIS. Paradoxical IRIS is defined as a clinical setting when a completely or partially treated opportunistic infection (OI) recurs or worsens following ART initiation and unmasking IRIS is defined as clinical activation of unrecognized or previously untreated OI (Sungkanuparph *et al*, 2010).

Sample size calculation

Since there were no reports of association between baseline CD4 cell count and outcome, the treatment outcome, including virologic response, was then used to estimate the sample size in our study. In a previous study from Thailand, 77% of HIV patients receiving ART had a virologic response (Maneesriwongkul *et al*, 2006); therefore, we estimated the virologic response of HIV patients after initiation of ART in this study to be 77% with a 95% confidence interval (CI) and the precision to be within 5% of the true value. A required sample size of at least 459 medical records of HIV patients was needed for our study.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using SPSS for Windows, version 18.0 (SPSS, Chicago, IL). Categorical variables were summarized as frequencies and percentages and analyzed by chi-square test or a Fisher's exact test where appropriate. Numerical variables were tested for normality using the Kolmogorov-Smirnov test. Numerical variables with non-normal distribution were summarized as median and interquartile range (IQR). Viral loads at each time point classified by baseline CD4 level categories were compared with the Mann-Whitney U test for two group comparison and the Kruskal-Wallis one-way ANOVA

for three groups or more. The time from initiation of ART to virologic response were assessed with the Kaplan-Meier estimates. The log-rank test was then used to compare between survival curves of different baseline CD4 categories. All tests for significance were 2-sided, with a $p<0.05$ indicating statistical significance.

RESULTS

A total of 576 medical records of HIV patients were reviewed; 112 were excluded because 64 patients did not received GPO-VIR-S or GPO-VIR-Z, 17 patients had insufficient data and 31 patients received ART prior to the study period. Thus, a total of 459 medical records met study criteria. Approximately half the patients were males (57.3%, 263/459), married (52.7%, 242/459) with a median (IQR) age of 38 (33-45) years. Most of the patients (96.9%, 445/459) presented with opportunistic infections (OIs), including mixed OIs (58.0%, 266/459), tuberculosis (21.8%, 97/445), candidiasis (6.1%, 27/445), herpes infection (2.0%, 9/445), pneumocystis pneumonia (1.6%, 7/445), toxoplasmosis (1.6%, 7/445), cryptococcosis (1.0%, 5/445) and other infections (6.1%, 27/445), such as salmonellosis, penicilliosis, nocardiosis, isosporiasis, histoplasmosis, cryptosporidiosis and *Mycobacterium avium* complex infection. The study subjects had co-infection with hepatitis B virus (13.9%, 64/459) and hepatitis C virus (23/261, 8.8%). The median (IQR) baseline CD4 cell count was 102 (40-212) cells/ l and HIV RNA was 180,675 (66,105-535,000) copies/ l. The median (IQR) baseline laboratory parameters were within normal limits. The baseline CD4 cell counts were then classified into three categories: ≤200, 201-350 and 351-500 cells/ l, in order to determine the appropriate baseline CD4

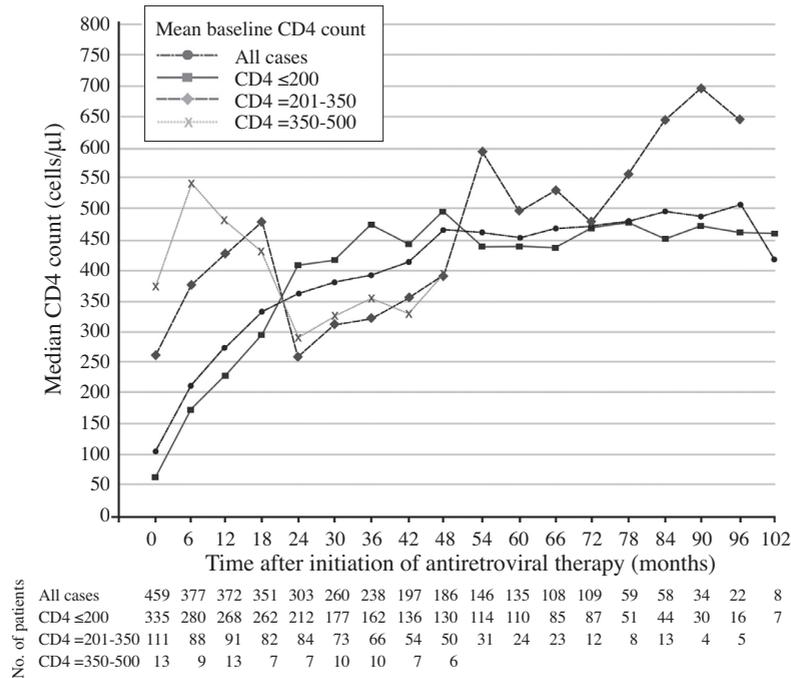| No. of patients																	
All cases	459	377	372	351	303	260	238	197	186	146	135	108	109	59	58	34	22	8
CD4 ≤200	335	280	268	262	212	177	162	136	130	114	110	85	87	51	44	30	16	7
CD4 =201-350	111	88	91	82	84	73	66	54	50	31	24	23	12	8	13	4	5	
CD4 =350-500	13	9	13	7	7	10	10	7	6									

Fig 1–Median CD4 cell count after initiation of ART.

cell count for optimizing treatment outcomes. The median hematocrit ($p<0.001$), white blood cell count ($p<0.001$) and platelet count ($p=0.046$) were significantly different among the three baseline CD4 categories (Table 1).

CD4 cell count changes after initiating ART

The median (IQR) CD4 cell count at baseline in our HIV patients [102 (40-212) cells/ l] increased to 213 (135-340) cells/ l at 6 months, 274 (183-403) cells/ l at 12 months and 423 (379-645) cells/ l at 102 months after initiation of ART. For subjects with a baseline CD4 cell count of ≤200 cells/ l, the median (IQR) CD4 cell count at baseline was 63 (27-122) cells/ l, this increased to 234 (156-319) cells/ l by 12 months, 403 (305-547) cells/ l at 24 months and maintained this level for 102 months after initiation of ART. For subjects with a baseline CD4 cell count of 201-350 cells/ l,

the median (IQR) baseline CD4 cell count was 258 (226-305) cells/ l; this increased to 431 (349-532) cells/ l at 12 months, 488 (366-579) cells/ l at 18 months and 257 (213-350) cells/ l at 24 months after initiation of ART. Thereafter, the CD4 cell count gradually increased until 102 months. For subjects with a baseline CD4 cell count of 351-500 cells/ l, the median (IQR) baseline CD4 cell count was 375 (365-387) cells/ l; this increased to 543 (409-622) cells/ l at 6 months, 485 (425-507) cells/ l at 12 months, and 437 (417-664) cells/ l at 18 months, 294 (163-312) cells/ l at 24 months and 395 (289-433) cells/ l at 48 months of ART (Fig 1).

Outcomes of HIV patients after initiation of ART

Treatment outcomes of HIV patients after initiation of ART including virologic response, virologic rebound, adverse effects

Table 1
Demographic and baseline characteristics of 459 adult HIV treatment naïve patients.

	Total		CD4 ≤ 200		CD4 201-350		CD4 351-500		p-value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Demographic and baseline characteristics									
Age (years)	459	38 (33-45)	335	38 (33-44)	111	38 (34-47)	13	35 (27-42)	0.191
Male, no. (%)	459	263 (57.3)	335	197 (58.8)	111	58 (52.3)	13	8 (61.5)	0.458
Married, no. (%)	459	242 (52.7)	335	173 (51.6)	111	63 (56.8)	13	6 (46.2)	0.575
OIs, no. (%)	459	445 (96.9)	335	328 (97.9)	111	104 (93.7)	13	13 (100.0)	0.066
HBV co-infection, no. (%)	459	64 (13.9)	335	46 (13.7)	111	18 (16.2)	13	0 (0)	0.273
HCV co-infection, no. (%)	261	23 (8.8)	195	17 (8.7)	61	5 (8.2)	5	1 (20.0)	0.667
Baseline laboratory parameters									
HIV RNA (copies/ml)	264	180,675 (66,105-535,000)	186	217,443 (73,282-525,250)	67	160,000 (55,000-541,000)	11	121,000 (17,600-557,000)	0.365
Hematocrit (%)	459	36.3 (32.5-39.3)	335	35.5 (31.9-38.8)	111	38.0 (34.6-40.5)	13	38.7 (36.7-46.4)	<0.001
White blood cell (x10^3/ l)	459	5.20 (4.02-6.50)	335	4.94 (3.89-6.14)	111	5.75 (4.66-6.79)	13	6.70 (5.68-8.17)	<0.001
Platelet counts (x10^3/ l)	459	260 (218-308)	335	257 (215-305)	111	261 (226-310)	13	307 (287-348)	0.046
Glucose (mg/dl)	92	90 (85-99)	68	89 (84-97)	22	95 (89-106)	2	97 (90-103)	0.102
BUN (mg/dl)	145	11 (9-13)	109	11 (9-13)	33	11 (9-12)	3	10 (8-10)	0.848
Creatinine (mg/dl)	193	0.9 (0.7-1.0)	141	0.9 (0.7-1.0)	48	0.8 (0.8-1.0)	4	0.9 (0.8-1.1)	0.805
AST (U/l)	285	29 (22-44)	214	31 (23-46)	66	27 (21-38)	5	32 (27-59)	0.054
ALT (U/l)	293	42 (33-63)	217	43 (34-61)	68	41 (30-62)	8	46 (26-83)	0.537
Albumin (g/dl)	220	4.1 (3.7-4.5)	167	4.0 (3.5-4.4)	50	4.3 (3.8-4.5)	3	4.2 (4.1-4.4)	0.047
Cholesterol (mg/dl)	218	175 (146-205)	159	169 (146-206)	54	180 (148-204)	5	203 (160-204)	0.601
Triglyceride (mg/dl)	73	133 (97-204)	53	130 (105-186)	18	159 (78-242)	2	134 (71-196)	0.826
HDL cholesterol (mg/dl)	19	35 (25-46)	10	36 (25-50)	8	36 (26-41)	1	-	0.689
LDL cholesterol (mg/dl)	17	130 (108-149)	9	130 (108-154)	7	124 (98-149)	1	-	0.596

IQR, interquartile range; OIs, opportunistic infections; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 2

Treatment outcomes of 459 adult treatment naïve HIV patients after initiation of ART in relation to baseline CD4 cell categories.

| Outcomes | CD4 categories | | | | | | | | p-value |
| | Total | | ≤ 200 | | 201-350 | | 351-500 | | |
	no./total	%	no./total	%	no./total	%	no./total	%	
Virologic response	449/459	97.8	329/335	98.2	108/111	97.3	12/13	92.3	0.327
Virologic rebound	74/449	16.5	53/329	16.1	20/108	18.5	1/12	8.3	0.626
Adverse effects	424/459	92.4	310/335	92.5	102/111	91.9	12/13	92.3	0.976
ART switching	349/459	76.0	248/349	74.0	90/349	81.1	11/349	84.6	0.245
Drug resistance	78/92	84.8	52/61	85.2	22/26	84.6	4/5	80.0	0.952
Paradoxical IRIS	81/459	17.6	65/335	19.4	13/111	11.7	3/13	23.1	0.160
Unmasking IRIS	62/459	13.5	46/335	13.7	14/111	12.6	2/13	15.4	0.937

ART, antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome

of ART, switching of ART, occurrence of drug resistance and occurrence of IRIS were determined. Our study showed the majority of patients (97.8%, 449/459) had a virologic response (Table 2). The Kaplan-Meier estimates showed the median (95% CI) time to achieve virologic response was 10.4 (9.8-11.0) months after initiation of ART (Fig 2a). The occurrence of virologic response was 98.2% (329/335) for a CD4 count of ≤200 cells/ l, 97.3% (108/111) for a CD4 count of 201-350 cells/ l and 92.3% (12/13) for a CD4 count of 351-500 cells/ l; the differences were not significant among the 3 groups (p=0.327) (Table 2). The Kaplan-Meier estimates showed the median (95%CI) time to achieve virologic response was 10.3 (9.7-11.0) months for a CD4 count of ≤200 cells/ l, 10.4 (9.0-11.8) months for a CD4 count of 201-350 cells/ l and 11.1 (8.4-13.7) months for a CD4 count of 351-500 cells/ l, the difference among these groups were not significant (p=0.401) (Fig 2b).

Of the 449 patients with a virologic response, 74 (16.5%) had virologic rebound (Table 2). The Kaplan-Meier estimates showed the median (95% CI) time to achieve virologic rebound was 30.0 (21.6-38.4) months after initiation of ART (Fig 3a). The occurrence of virologic rebound was 16.1% (53/329) for a CD4 count of ≤200 cells/ l, 18.5% (20/108) for a CD4 count of 201-350 cells/ l and 8.3% (1/12) for a CD4 count of 351-500 cells/ l; the differences between groups were not significant (p=0.626) (Table 2). The Kaplan-Meier estimates showed the mean (95% CI) time to the occurrence of virologic rebound for the three baseline CD4 categories was 30.0 (19.3-40.7) months for those with a CD4 count of ≤200 cells/ l, 24.0 (16.5-31.5) months for those with a CD4 count of 201-350 cells/ l and 36.0 months for those with a CD4 count of 351-500 cells/ l; the differences were not significant (p=0.562) (Fig 3b).

The majority of patients had adverse effects due to ART (92.4%, 424/459); these included lipodystrophy (12.3%, 52/424), bleeding (7.3%, 31/424), bone marrow suppression (6.4%, 27/424), hyperlipidemia (2.6%, 11/424), hypersensitivity (2.6%, 11/424), hepatotoxicity (1.2%, 5/424),
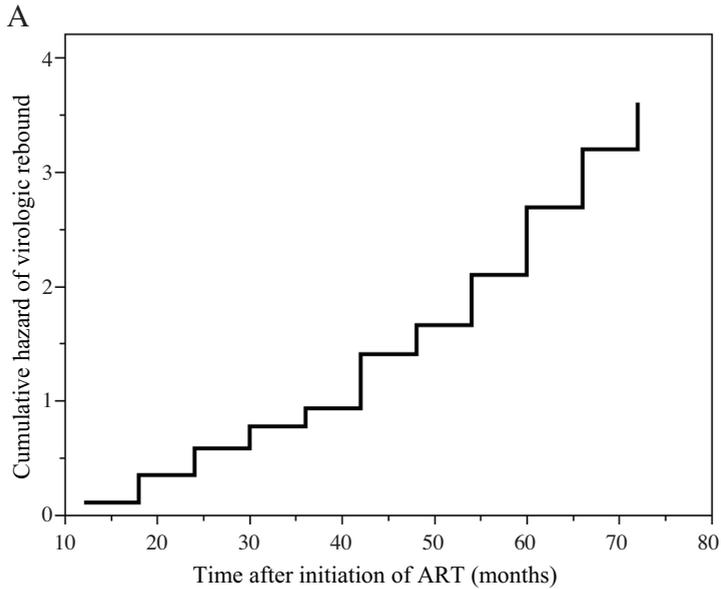
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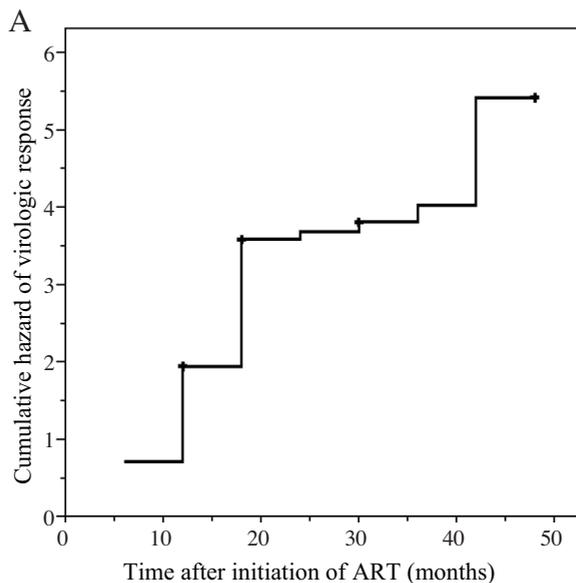
Time (months)	6	12	18	24	30	36	42
No. of cumulative events	232	393	443	444	445	446	449

B
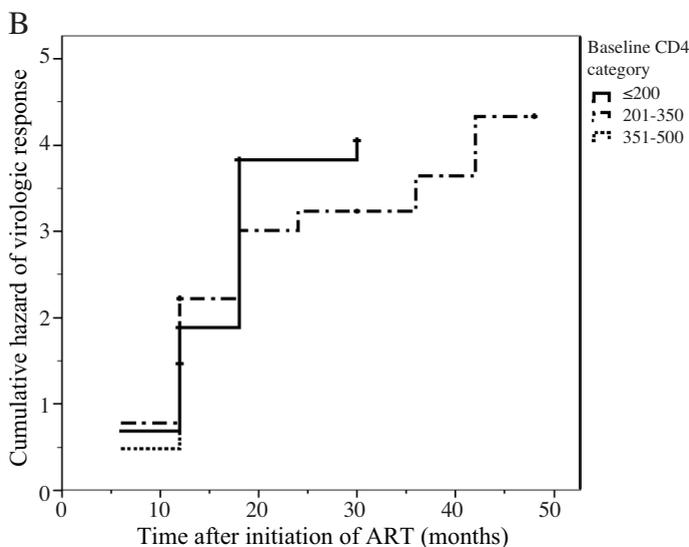
	Cumulative number of virologic responses at different times								
Time (months)	6	12	18	24	30	36	42	Median	95%CI
CD4≤200 (*n*=335)	167	284	326	326	327	327	329	10.3	9.7-11.0
CD4=201-350 (*n*=111)	60	99	105	105	106	107	108	10.4	9.0-11.8
CD4=351-500 (*n*=13)	1	6	11	-	-	-	-	11.1	8.4-13.7

Fig 2–Kaplan-Meier estimates of cumulative hazard to virologic response among 459 treatment naïve HIV patients after initiation of ART (A) with median (95%) time of 10.4 (9.8-11.0) months (B) summarized by baseline CD4 categories.

A

Time (Month)	6	12	18	24	30	36	42	48	54	60	66	72	78
No. of cumulative events	0	8	22	33	40	45	56	60	65	69	71	72	74

B
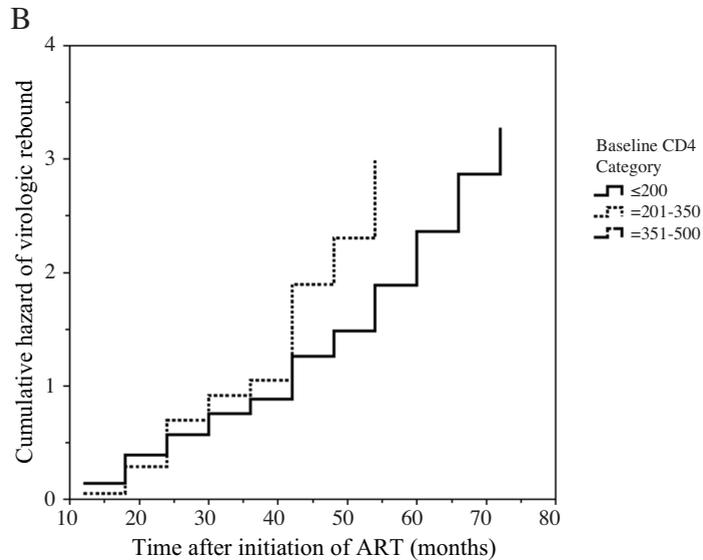
	Cumulative number of virologic rebound at different times									
Time (months)	6	12	18	24	30	36	42	48	Median	95% CI
CD4≤200 (n=335)	0	7	17	23	28	31	38	41	30.0	19.3-40.7
CD4=201-350 (n=111)	60	99	105	105	106	107	108	108	24.0	16.5-31.5
CD4=351-500 (n=13)	1	6	11	-	-	-	-	-	36.0	-

Fig 3–Kaplan-Meier estimates of cumulative hazard to virologic rebound among 459 treatment naïve HIV patients after initiation of ART (A) with median (95% CI) response time of 30.0 (21.6-38.4) months (B) summarized by baseline CD4 categories.

peripheral neuropathy (0.7%, 3/424) and diabetes mellitus (0.2%, 1/424). Two-thirds of these patients (66.5%; 282/424) had ≥2 adverse effects. The percents of patients were adverse effects among the three baseline CD4 categories were: 92.5% (310/335) for a CD4 count ≤200 cells/ l, 91.9% (102/111) for a CD4 count of 201-350 cells/ l and 92.3% (12/13) for a CD4 count of 351-500 cells/ l; these differences were not significant (*p*=0.976) (Table 2).

Seventy-six percent of 459 patients (349/459) had a switch in ART. The percents of those who switched ART by baseline CD4 category were 74.0% (248/349) for a CD4 count ≤200 cells/ l, 81.1% (90/349) for a CD4 count of 201-350 cells/ l and 84.6% (11/349) for a CD4 count of 351-500 cells/ l; these differences were not significant (*p*=0.245) (Table2). The Kaplan-Meier estimates showed the median (IQR) times to switching the ART among the three baseline CD4 categories were: 23.0 (11.5-43.6) months for a CD4 count of ≤200 cells/ l, 21.5 (5.7-36.6) months for a CD4 count of 201-350 cells/ l and 10.0 (1.1-15.8) months for a CD4 count of 351-500 cells/ l; these differences were not significant (*p*=0.097).

Of the 459 patients, 92 genotype testing due to a clinical suspicion of drug resistance; 78 of these patients (84.8%) had drug resistance. The occurrence of the drug resistance by baseline CD4 count were 85.2% (52/61) for a CD4 count of ≤200 cells/ l, 84.6% (22/26) for a CD4 count of 201-350 cells/ l and 80.0% (4/5) for a CD4 count of 351-500 cells/ l; these differences were not significant (*p*=0.952). After initiation of ART, 31.2% of patients (143/459) developed IRIS, which included paradoxical IRIS (17.6%, 81/459) and unmasking IRIS (13.5%, 62/459). The occurrence of paradoxical IRIS by baseline CD4 count

were: 19.4% (65/335) for a CD4 count of ≤200 cells/ l, 11.7% (13/111) for a CD4 count of 201-350 cells/ l and 23.1% (3/13) for a CD4 count of 351-500 cells/ l; these differences were not significant (*p*=0.160). The percents of unmasking IRIS by CD4 level were: 13.7% (46/335) for a CD4 level of ≤200 cells/ l, 12.6% (14/111) for a CD4 level of 201-350 cells/ l and 15.4% (2/13) for a CD4 level of 351-500 cells/ l; these differences were not significant (*p*=0.937) (Table 2).

DISCUSSION

This retrospective study was conducted to assess the association between baseline CD4 cell count and outcomes among HIV patients after initiation of a fixed dose anti-HIV regimen of GPO-VIR-S or GPO-VIR-Z. The median CD4 cell count increased to >350 cells/ l by 24 months and continued to increase for 3 years after initiation of ART, similar to previous studies (Staszewski *et al*, 1999; Bonjoch *et al*, 2006; Gras *et al*, 2007; Le Moing *et al*, 2007; Moore *et al*, 2007; Manosuthi *et al*, 2008; Nash *et al*, 2008).

In our study, patients with baseline CD4 cell count ≤200 cells/ l had greater CD4 cell count change from baseline by 24 months, similar to previous studies showing a lower baseline CD4 cell count was associated with a greater increase in CD4 cell response (Hunt *et al*, 2003; Nash *et al*, 2008). A virologic response occurred in 97.8% of patients and the median time to achieve virologic response was 10.4 months after initiation of ART. Among patients who had virologic response, 16.5% had virologic rebound with a median time to rebound of 30.0 months after initiation of ART. Our findings are similar to a previous study showing 90% of treatment naïve HIV patients achieved virologic

response after initiation of ART, but 20.6% had virologic rebound 9 months after virologic response (Touloumi *et al*, 2008). Another study showed the median time to virologic response was 6 months after initiation of ART, shorter than our study (MacArthur *et al*, 2006). The percents of virologic response and virologic rebound were not associated with baseline CD4 cell count and the median time to achieve virologic response or virologic rebound was not different by CD4 count. Our findings are similar to a previous study (Kilaru *et al*, 2006).

Adverse effects of ART occurred in 92.4% of patients and required a switch in ART in 76% of patients due to the adverse effects of ART. Adverse effects of ART and the need to switch ART were not associated with baseline CD4 level. Of the 92 patients who had genotype testing done due to clinical suspicion of drug resistance, 84.8% had drug resistance; there were no differences in drug resistance by baseline CD4 count. IRIS occurred in 31.2% of patients in our study, similar to previous reports ranging from 15-45% (French *et al*, 2004; Jevtovi *et al*, 2005; Shelburne *et al*, 2006; Manabe *et al*, 2007); there were no differences by baseline CD4 count.

In conclusion, the outcomes of HIV patients in our study did not differ by baseline CD4 cell count.

ACKNOWLEDGEMENTS

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